**REMARKS**

Claims 42 and 47 are amended herein to delete the "about" with respect to the lower limit of the antibody concentration range. In addition, claim 45 to human therapy is incorporated into claim 42, hence the cancellation of claim 45 as moot. Entry of the present amendment under Rule 116 is respectfully requested, given that the amendment is made to expedite allowance or simplify issues for appeal. Moreover, Applicants note that the present final Office Action issued immediately following the filing of a RCE accompanied by an amendment, so Applicants respectfully request the Examiner permit entry of the present amendments.

In the Office Action mailed September 12, 2005, the Examiner retains the rejection of claims 42 and 44-47, 51 and 52 under 35 USC Section 103(a) as being obvious over US Patent No. 5,770,195 in view of US Patent No. 5,720,954, and Burton *et al. Am J. Vet. Res* 42(20):308-310 (1981).

The Examiner maintains the rejection on the basis that "[if] a *prima facie* case of obviousness is established, the burden shifts to the applicant to come forward with arguments and/or evidence to rebut the *prima facie* case."

Applicants submit that the Examiner has clearly failed to establish a *prima facie* case of obviousness based on the cited references - the burden remains with the PTO to make out the *prima facie* case.

In particular, Applicants submit that the Examiner has failed to demonstrate how the claimed (1) antibody concentration and (2) subcutaneous administration, would have been obvious from the cited art.

(1) HER2 antibody concentration

The claims herein refer to administration of a formulation comprising an antibody which binds HER2 receptor in an amount of 80 mg/mL to about 400mg/mL. The primary reference - the '195 patent - refers to HER2 antibodies "typically formulated in such vehicles at concentrations of about 1 mg/ml to 10mg/ml" (col. 12, lines 3-4).

The Examiner has previously held that "the claimed ranges and prior art ranges do not overlap but are close enough that one skilled in the art would have

expected them to have the same properties" (6/30/04 Office Action, paragraph bridging pages 3-4). Applicants submit that one skilled in the art would not have expected formulations with 1-10 mg/mL antibody (as in the '195 patent) as compared to formulations with 80-400mg/mL antibody (the present invention) would have the same properties. The present application demonstrates that attaining the presently claimed high antibody concentrations in a stable pharmaceutical formulation required inventive activities. See pages 2-5 and the Examples in the present specification. Moreover, the claims herein are method of treatment claims, and clearly the high antibody concentration formulation administered according to the presently claimed method would have a different effect than that of the '195 patent.

Now, the Examiner suggests that the *prima facie* case of obviousness is "based on overlapping ranges" (9/12/05 Office Action, page 4, lines 3-4). However, Applicants submit this is based on an erroneous comparison of the ranges in the art with that of the present claims - certainly 1-10 mg/mL antibody (as in the '195 patent) does not overlap with 80-400mg/mL antibody (as in the present claims).

At page 4 of the present Office Action, the Examiner states that 'the claims as interpreted based on the recitation of the term "about," opens the range of the dosage to any range.' Without acquiescing in this interpretation, and purely in the interests of expediting prosecution, Applicants have amended claims 42 and 47 herein by deleting the "about" with respect to the lower limit (80mg/mL) of the range.

In any event, even if the claimed ranges did overlap, Applicants submit that the presently claimed high antibody concentrations in the formulation are shown to have unexpected beneficial properties. As noted on page 2, lines 16-20, such high antibody concentrations in the formulation were found to be particularly useful when the formulation was to be subcutaneously administered. Moreover, despite the very high antibody concentration in the formulation, it was found to be stable and pharmaceutically acceptable. This was not disclosed in the cited references. Hence, the presently claimed high antibody concentration is associated with unexpected results, both in terms of the ability to achieve stable pharmaceutically-tolerable formulations (in spite of the high antibody concentration), as well as the method of treatment that can be carried out using the formulation.

Applicants submit that claims 42 and 47 are patentable over the cited art for reciting the high HER2 antibody of 80 mg/mL to about 400mg/mL which is much higher than that set forth in the cited art, namely the range of 1-10 mg/ml, antibody. Moreover, the claims herein concern subcutaneous administration of such a high antibody concentration formulation, yet further distinguishing over the cited art.

(2) Subcutaneous administration

In addition to the high HER2 antibody concentration in the formulation, as discussed above, the claims herein concern subcutaneous (SQ) administration of such formulation. The '195 patent, on the other hand, does not specifically refer to SQ administration, calling out intravenous (IV) administration instead (col. 11, line 51). The Examiner has urged that SQ administration would be an optimization of IV administration - no prior art or objective evidence is relied on to support this conclusion. Hence, Applicants submit that the burden remains with the PTO to substantiate its claim that SQ would represent an optimization of IV for cancer therapy with a HER2 antibody.

Applicants submit that SQ administration of a HER2 antibody for cancer therapy would not be considered an optimization of IV administration. At the time of filing the above application, therapeutic antibodies for cancer therapy were administered IV. The Examiner points to absolutely no evidence to show that SQ alternative would be considered a viable *alternative* to IV administration, let alone an optimization in the context of the present claims which concern therapy of cancer with a HER2 antibody.

Applicants submit that, since the Office has failed to make out a *prima facie* case of obviousness as to SQ administration of the HER2 antibody formulation as claimed herein, the rejection should be reconsidered and withdrawn for this additional reason.

The Secondary Reference

The Examiner relies on secondary reference, Burton et *al.* from the *American Journal of Veterinary Research*. Applicants submit this is not analogous art, being related to providing *equine serum* for *animal feed* rather than a *therapeutic HER2 antibody* for *cancer therapy* in *humans*. The present claims require subcutaneous administration of a stable, pharmaceutically acceptable

formulation of a HER2 antibody. Applicants submit that the skilled person would not look to the Burton reference as providing any guidance whatsoever as to whether one can make the presently claimed high antibody concentration HER2 antibody formulation, let alone whether such administration could or should be administered SQ to human cancer patients. The information that Burton provides concerning equine serum feedstock for neonatal foals is simply irrelevant to the presently claimed invention. Hence, Applicants dispute that there is any basis for combining the '195 patent with Burton as the Examiner has done.

Applicants submit that the above discussion shows how the presently claimed invention is distinguished over the art, and respectfully request reconsideration and withdrawal of the Section 103 rejection.

Early receipt of a notice of allowance is awaited.

Respectfully submitted,
GENENTECH, INC.

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By: _____
Wendy M. Lee
Reg. No. 40,378
Telephone: (650) 225-1994